A phase II monocentric study of oxaliplatin in combination with gemcitabine (GEMOX) in patients with advanced/metastatic transitional cell carcinoma (TCC) of the urothelial tract


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Received 30 August 2005; revised 10 January 2006; accepted 20 February 2006

Background: The aim of the study was to evaluate the activity and the safety of the gemcitabine–oxaliplatin (GEMOX) combination as first-line treatment in advanced/metastatic transitional cell carcinoma (TCC) of the urothelial tract.

Materials and methods: Patients with metastatic or unresectable TCC, PS ≤2, creatinine ≤1.5 upper limit of normal range (UNL) and measurable disease according to RECIST criteria were treated with a combination of gemcitabine (1500 mg/m²) followed by oxaliplatin (85 mg/m²) on day 1 and 15 of a 28-day cycle.

Results: A total of 123 cycles were administered to 30 patients (median 4, range 1–8). Three complete responses (CR) and 11 partial responses (PR) were observed. Overall response rate (ORR) was 47% (95% CI 28% to 66%). Median overall survival (OS) was 15 months (95% CI 8–31). Grade 3 and 4 neutropenia were reported in three and one patient, respectively; grade 3 anaemia in three patients; grade 3 and 4 thrombocytopenia in two and one patient, respectively; grade 1, 2 and 3 peripheral neuropathy in 14, 11 and two patients, respectively; grade 2 and 3 fatigue in 13 and seven patients respectively.

Conclusions: The GEMOX combination is active in advanced/metastatic TCC with minimal toxicity and needs to be evaluated in a selected population of unfit patients and compared with other non-cisplatin-containing regimens.

Key words: urothelial tract carcinoma, bladder cancer, chemotherapy, gemcitabine, oxaliplatin

Introduction

Clinical trials of metastatic urothelial cancer have shown that this disease is highly sensitive to chemotherapy [1, 2]. The combination of methotrexate, vinblastine, adriamycin and cisplatin (MVAC) yields a median survival of approximately 12–14 months [3]. Of note is the toxic death rate associated with this regimen (3%–4% across randomised trials), which must be weighed against a poor 5-year survival rate (5.8%) [3, 4].

During the last decade, gemcitabine, a novel nucleoside analogue, has been recognised as an active drug in advanced urothelial cancer [5–7]. Cisplatin plus gemcitabine were compared with MVAC in a randomised phase III trial of 400 patients, which showed that MVAC was associated with higher rates of neutropenic sepsis (12% versus 1%), febrile neutropenia (49% versus 9%) and grade 3/4 mucositis (22% versus 1%). Overall response, progression-free survival and 5-year overall survival were about the same, suggesting that the cisplatin–gemcitabine combination might be a reasonable alternative to MVAC therapy [8, 9]. Another phase III study compared ‘high-dose’ MVAC (administered every 2 weeks) with standard MVAC (administered every 4 weeks) in 263 patients. It demonstrated better overall survival for the biweekly regimen with a similar toxicity profile in both arms [10].

Both the cisplatin–gemcitabine regimen and high-dose MVAC are considered as reference regimens for patients with advanced/metastatic urothelial carcinoma. However, this disease occurs in an older patient population and carboplatin is frequently used in combination therapy because its toxicity profile is more favourable. To address the question of whether carboplatin and cisplatin are equally effective in this disease, a phase II study compared gemcitabine plus either cisplatin or carboplatin in 113 patients with advanced or metastatic urothelial cancer. Renal toxicity was greater in the cisplatin arm (25% versus 16%), but only grade 1/2 events were observed. Patients who received carboplatin required more frequent red blood cell and platelet transfusions due to myelosuppression. Perhaps most notably, more patients in the cisplatin arm achieved a complete response (22.7% versus

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was administered in a 30-min i.v. infusion followed by a 6-h i.v. infusion.

Oxaliplatin, a diaminocyclohexaneplatinum, was recently introduced into clinical practice because of its activity in several solid tumour types [12]. As a supra-additive effect was demonstrated with the gemcitabine–oxaliplatin combination in several human cancer cell lines [13], a phase I/II study of the doublet, known as the GEMOX combination, was performed in our institution in patients with either non-small-cell lung cancer or ovarian carcinoma, in which good tolerance and promising activity were shown [14]. The primary objective of the study was the evaluation of the response rate of the same combination in advanced transitional cell carcinoma of the urothelium. The study was approved by the Committee for the Protection of Persons Undergoing Biomedical Research according to French law and by the Institutional Review Board according to Institutional rules.

materials and methods

patients

This study enrolled patients with pathologically-confirmed metastatic or unresectable transitional cell carcinoma (TCC) of the urothelium (renal pelvis, ureter, bladder or urethra), who were chemotherapy naive. Eligibility criteria included an ECOG performance status ≤2, a measurable lesion ≥20 mm, absolute granulocyte count >1500/µl, platelet count ≥150 000/µl, bilirubin <1.5 the upper limit of normal range (ULN), alkaline phosphatase and transaminases ≤3 ULN in the absence of liver metastases and ≤5 ULN in case of liver metastases, creatinine ≤1.5 ULN, clinically normal cardiac function and a signed informed consent.

treatment plan

Hospitalisation was not required for treatment. Gemcitabine (1500 mg/m²) was administered in a 30-min i.v. infusion followed by a 6-h i.v. infusion of oxaliplatin (85 mg/m²) on days 1 and 15 of a 28-day cycle. Treatment was pursued until complete response plus one cycle or partial response allowing local treatment with a curative intent or disease progression or limiting toxicity, or if the patient and/or the investigator chose to stop treatment in the event of stable disease.

definition of response

Response to treatment was assessed in all patients included in the study. The assessment of activity was based on the response rate (RR) according to RECIST criteria. A complete response (CR) was defined as the complete disappearance of all target lesions. A partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter (LD) of target lesions with the baseline sum of the LD of target lesions as the reference. Progressive disease was defined as at least a 20% increase in the sum of the LD of target lesions. The duration of response was measured from the date of the start of treatment to the date of documented progression.

toxicity criteria

Toxicity was evaluated in all patients who started treatment. Toxicity was graded according to the National Cancer Institute toxicity criteria (version 2.0). Dose and schedule modifications were based on weekly blood counts and 2 weekly assessments of clinical toxicity. The worst grade of toxicity was recorded for each cycle. In case of haematological (grade ≥2) or non-haematological toxicity (grade ≥3), treatment was interrupted until the resolution of symptoms. In case of grade ≥2 haematological toxicity, oxaliplatin was reduced to 65 mg and gemcitabine to 1200 mg/m². Any grade 4 toxicity led to withdrawal of the patient from the study.

follow-up and outcomes

Physical examinations and baseline blood tests were repeated at 2-week intervals. Imaging studies to define disease extent were undertaken at 8-week intervals, and repeated after 4 weeks to establish a response. The primary end point was the objective response (OR) rate. The secondary end points were the duration of response, overall survival and tolerance. All patients included in the study were included in the analysis of response and of survival, and all treated patients were included in the evaluation of toxicity.

statistical methods

The aim of this trial was to decide whether the gemcitabine–oxaliplatin combination should be investigated further in locally advanced or metastatic urothelial cancer, based on the following criteria: (1) if the results of the trial were compatible with a 60% response rate in the population under study, the combination would be further investigated; (2) however, if the results were unable to demonstrate at least a 30% response rate in the population under study, the combination would be rejected for further investigation.

The primary end point was the response rate according to RECIST criteria. The secondary end points were the duration of response according to RECIST criteria, overall survival and tolerance. The two-stage accrual design described by Simon [15] was chosen to determine the total number of patients required for the study with a type I error = 0.08 and a type II error = 0.05. A preliminary test was planned to assess 13 patients. The study was to be stopped if less than five responses were observed. Otherwise, 15 additional patients were to be recruited for a second stage. If at least 12 responses were observed out of a total of 28 patients, the conclusion was to be that the combination deserved further investigation. Treatment results are expressed as percentages with 95% confidence intervals (CI) or as medians and ranges. Time to progression (TTP), overall survival (OS) and progression-free survival (PFS) were estimated by the Kaplan–Meier method and calculated from the day treatment started with Rothman’s confidence intervals [16].

results

From February 2002 to July 2004, the study was completed with 30 patients enrolled onto the study since seven OR had been observed at the end of the first stage in the first 13 patients.

patient and treatment characteristics

Baseline patient characteristics are summarised in Table 1. Thirty patients were enrolled with a median age of 65 (range 41–83). There were 25 men and five women. Sixteen patients presented with visceral metastases. Median creatinine clearance was 70 ml/min (range 35–136) but it was less than 60 ml/min in eight patients. Patients were classified according to Bajorin’s prognostic groups based on the PS and the presence of visceral metastases in one or several sites in subjects with advanced urothelial cancer [17]. Twelve patients had undergone radical surgery with a curative intent before (a radical cystectomy in eight patients, a nephro-ureterectomy in four patients) and 18 patients had metastatic disease or were...
inoperable because of loco-regional disease extension at diagnosis.

activity

Treatment activity was assessed in the first 13 patients as stipulated by the statistical methodology. Seven OR were achieved, therefore the second step of the study was carried out. Cerebral metastases were discovered in one patient during the first cycle. This patient was not treated according to the protocol thereafter but he was evaluated as a treatment failure. Fourteen patients achieved an objective response, including three CR and 11 PR. The overall response rate (ORR) was 47% (95% CI 28% to 66%). The median duration of response was 11 months (95% CI 3–13). At the time of the analysis, 18 patients had died with a median follow-up of 26 months (range 13–32) [18]. Two patients were alive in CR after GEMOX chemotherapy, nine patients were alive with disease and one patient was alive in CR after salvage chemotherapy with MVAC. Sixteen patients died of disease progression and two patients died as a result of the toxicity of salvage treatment. The two patients who were alive with no evidence of disease after GEMOX at 30 months and 26 months, respectively, both had involved abdominal nodes, at the diagnosis of bladder cancer and after a cystectomy, respectively. Another patient was alive with no evidence of disease after salvage by MVAC.

Table 1. Patient characteristics (number of patients = 30)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median 65</td>
</tr>
<tr>
<td></td>
<td>Range 41–83</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 25 (75)</td>
</tr>
<tr>
<td></td>
<td>Female 5 (25)</td>
</tr>
<tr>
<td>Creatine clearance</td>
<td>70 (33–136)</td>
</tr>
<tr>
<td>Bajorin’s prognostic groups</td>
<td>1: 14</td>
</tr>
<tr>
<td></td>
<td>2: 11</td>
</tr>
<tr>
<td></td>
<td>3: 5</td>
</tr>
<tr>
<td>Previous radiotherapy</td>
<td>No 29 (97)</td>
</tr>
<tr>
<td></td>
<td>Yes 1 (3)</td>
</tr>
</tbody>
</table>

Table 2. Response according to diseased sites (number of patients = 30)

<table>
<thead>
<tr>
<th>Diseased sites</th>
<th>Complete response (%)</th>
<th>Partial response (%)</th>
<th>Overall response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>3 (60)</td>
<td>3 (60)</td>
<td></td>
</tr>
<tr>
<td>Pelvic masses</td>
<td>2 (28)</td>
<td>1 (14)</td>
<td>3 (42)</td>
</tr>
<tr>
<td>Retroperitoneal nodes</td>
<td>9 (64)</td>
<td>9 (64)</td>
<td></td>
</tr>
<tr>
<td>Mediastinal nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>1 (1.25)</td>
<td>1 (1.25)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>2 (66)</td>
<td>2 (66)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The median progression free survival was 7 months (95% CI 3–14). There were three OR in visceral metastases which were partial: in the lung in two patients and in the liver in one patient. PFS at 2 years was 10 months (95% CI 3% to 30%). Median overall survival was 15 months (95% CI 8–31). OS at 2 years was 30% (95% CI 15% to 53%). OS and PFS curves are shown in Figure 1.

administration of therapy and toxicity

A total of 123 cycles of protocol treatment were administered to 30 patients, with a median number of four cycles per patient (range 1–8). Nineteen patients (67%) completed at least four cycles of treatment. No treatment-related death occurred. Thirty patients were assessed for toxicity. On the whole, therapy was well tolerated. Haematological toxicity is summarised in Table 3. Grade 3 and 4 neutropenia were reported in three patients and one patient, respectively, grade 3 anaemia in three patients, grade 3 and 4 thrombocytopenia in two and one patient, respectively. Grade 1, 2 and 3 peripheral neuropathy in 14, 11 and two patients, respectively, grade 2 and 3 fatigue in 13 and seven patients, respectively, grade 2 mucosal toxicity in two patients. One patient experienced grade 2 renal toxicity after the first cycle of treatment but it was due to ureteral obstruction related to disease progression and not to chemotherapy. Median creatinine clearance after treatment was 70 ml/mn (range 33–157). Hospitalisation due to febrile neutropenia was required in two patients and red blood cell transfusion in one patient. Discontinuation of chemotherapy was due to ineligibility in one patient, a CR plus one cycle according to the protocol in three patients, a PR allowing further local treatment with a curative intent according to the protocol in two patients, progression in 12 patients, toxicity in five patients, treatment duration that was found long enough even though there was no limiting toxicity in seven patients (by patient’s decision in three patients and by the investigator’s decision in four patients). Clearly, the limiting toxicities were fatigue and peripheral neuropathy, which occurred after the fourth cycle.

discussion

The primary end point was the activity of the combination. We therefore chose to enrol fit patients with a PS ≤2 in order to
complete a monocentric phase II trial within a limited time period and avoid patients with a PS ≥2 in whom a high drop-out rate would have been expected, given the narrow therapeutic window in such patients. Most of the patients included in the present study might therefore have been eligible for cisplatin-based chemotherapy. Indeed, as there was no renal toxicity and little haematological toxicity with the GEMOX combination, they were offered salvage treatment with MVAC if treatment failed.

To the best of our knowledge, only one report on the GEMOX combination has previously been published on advanced urothelial cancer. The regimen was the same as in our study. The study included 20 patients, seven of whom had received previous chemotherapy. The primary end point was feasibility. While the treatment was well tolerated, data on efficacy were scarce: two PR were achieved in pretreated patients and two PR in chemotherapy-naïve patients with a median duration of response of 3 months [19]. One other report was only published as an abstract [20]. The study regimen was a combination of gemcitabine (1200 mg/m²) and oxaliplatin (100 mg/m²). It was well tolerated and six PR were reported in 12 patients.

Other gemcitabine–oxaliplatin schedules have been published [21, 22]: in a study performed in patients with hepatocellular carcinoma comparing two schedules of the combination, it was concluded that the combination of gemcitabine (1000 mg/m²) and oxaliplatin (100 mg/m²) was better tolerated than the combination of gemcitabine (1500 mg/m²) and oxaliplatin (85 mg/m²) [21].

Irrespective of the precise treatment regimen, the GEMOX combination is efficient in urothelial cancer. The best phase II trial of gemcitabine used alone yielded a 29% RR in chemotherapy-naïve patients [5–7]. Therefore, there is a borderline possibility that the 47% ORR could be attributed to gemcitabine alone considering the 95% CI of 28% to 66%. However, the same comment could be applied to MVAC chemotherapy given the results obtained at the Princess Margaret hospital, i.e. a median ORR of 40% (CI 95% 23% to 59%) [3]. Only controlled trials can provide an answer to questions concerning the superiority of one chemotherapy regimen over another but, for ethical as well as economic considerations, controlled trials cannot be launched without prior phase II studies. Therefore, it can be concluded from this study that oxaliplatin most probably exerted an additive effect on gemcitabine. However, considering the ORR of most studies of cisplatin-based combinations, it is unlikely that the GEMOX combination could ever be proven superior or even on a par with cisplatin-based combinations. We confirmed the good haematological and renal tolerance of the combination. The GEMOX combination could therefore be investigated in a selected population of so called ‘unfit’ patients with impaired renal function, comparing it with other combinations used in those patients to determine its potential role. To date, the combinations most widely used are based on carboplatin, either methotrexate–vinblastine–carboplatin or gemcitabine–carboplatin [23] or paclitaxel–carboplatin [24].

Combinations of gemcitabine and paclitaxel have also been used as first-line chemotherapy in such patients [25]. All of these combinations are feasible in the outpatient clinic. However, both carboplatin-based regimens and the paclitaxel–gemcitabine combination give rise to myelotoxicity, which usually limits the administration of chemotherapy. Furthermore, the role of taxanes in urothelial cancer has been challenged by a randomised study, which showed the inferiority of the docetaxel–cisplatin combination versus MVAC [26].

The GEMOX combination should, therefore, be studied in a population of unfit patients and compared with the reference regimens for unfit patients, which could be either methotrexate–vinblastine–carboplatin or gemcitabine–carboplatin, according to the results of the ongoing trial of the EORTC comparing these two combinations [27]. Suggested end points are ORR, OS, number of days of hospitalisation and quality of life, thereby allowing a comparative benefit/risk study.

acknowledgements

The authors thank Ms Lorna Saint Ange for editing.

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